Review

Maternal schistosomiasis: a growing concern in sub-Saharan Africa

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Schistosomiasis remains one of the most important tropical parasitic infections threatening millions of lives in endemic areas. Cases of infections due to *Schistosoma* spp, the diecious digenetic trematodes have been on the increase over the last decades. While considerable efforts have been made to reduce infections and morbidities in most endemic areas, these efforts seem to be tailored only towards a specific group (school-based resources). This bias towards school children in epidemiological studies has also been observed in various research efforts in sub-Saharan Africa, thus making it difficult to produce a reliable estimate of the extent of infection in other strata of the population at risk. In recent times, attention has been drawn to *Schistosoma* spp infections in infants and preschool children, while studies on epidemiology of maternal schistosomiasis still suffer neglect. Considering the potential morbidity of *Schistosoma* infections on the mothers, fetuses, and neonates, as evidenced in some animal models and human case studies, more attention is solicited in all areas of observational studies and clinical trials, for maternal schistosomiasis with the aim of providing relevant data and information for effective management of the disease during pregnancy.

Keywords: Schistosomiasis, Pregnancy, Neonatal health, Public health concern

Introduction

Schistosomiasis still remains a serious threat in the developing world. With the current level of public awareness and policies already in place to abate the morbidity of *Schistosoma* infection in affected regions, little or no progress has been achieved, as no significant reduction in morbidity level was recorded between the last and current decades in most endemic regions.[1,2] In fact, countries such as Burkina Faso, Guinea, Mauritania, Nigeria, Senegal, and Togo have witnessed a significant increase in infection level in the recent estimate.[2]

Control measures had been targeted at different stages based on the knowledge of factors of epidemiological importance with limited successes. Primed among these is the presence of snail intermediate hosts which harbor the immature stages of the parasite. The introduction of some exotic potential snail hosts species, not originally native to some endemic areas, could have worsened the situation.[3] The dynamics of the socio-cultural and socio-demographic factors, such as age, sex, education, religion, and water use pattern, among others, have also been reported to be associated with schistosomiasis.[4–7]

One of the major problems hampering effective management of schistosomiasis in endemic countries is the problem of reinfection. Targeted control on school children is often advocated and is usually the main operation in sub-Saharan Africa[8] due to limited resources. However, exclusion of other groups, often times comprising the adult population, makes reinfection almost inevitable in low resource rural endemic regions of developing countries. These neglected groups (pregnant women are inclusive) which are believed not to be sufficiently exposed to infection and often left untreated could serve as reservoirs of infection, bringing the distribution of the disease to pre-control level over time.

Apart from serious consequences other untreated members of a population with schsitosomiasis may suffer, the effects of the disease on pregnant women seem to be greater, as infection will jeopardize not only the well-being of the mothers but also the growing fetuses.[9] It is therefore imperative to include pregnant women in the control programs even when resources are limited. Nevertheless, the meager baseline epidemiological data on schistosomiasis during pregnancy could hamper or slow down control in the group. This review, therefore, reports the available

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DOI 10.1179/2047773214Y.0000000150

data on prevalence of maternal schistosomiasis over the last decades; it discusses the problems associated with infection and the administration of drugs during pregnancy. It also advocates for more research in maternal schistosomiasis, to provide policy makers with adequate information for the best control strategies in the group.

Schistosomiasis: A Case of Neglect in Tropical Countries

The stories about the epidemiology of schistosomiasis have been inconsistent, with success stories in some parts of the world, but failure and progressive spread to new areas in other parts. While successful control has been achieved in Tunisia and Japan, the disease is near elimination in Morroco and some Carribean islands.[10–12] Brazil, China, and Egypt have also achieved considerable progress towards elimination of the disease.[13–15] In sub-Saharan Africa, however, many countries have witnessed persistent rise in infection in the recent estimate.[2] The increased demand for development of water resources and lack of proper disease surveillance in these artificial lakes have been associated with several schistosomiasis outbreaks in many African countries.[5]

Despite the burden of schistosomiasis and its public health importance, the disease has been neglected for many years, due to the following interrelated factors: the focal distribution of the disease and its confinement to the tropics and subtropics[16,17] and the marginalization of poor rural and urban communities, making their voices not to be heard sufficiently, so as to establish this disease firmly within a national political agenda.[18] Moreover, the subtleness and chronic nature of schistosomiasis makes it of less priority at the national and global strategic plans compared to diseases such as malaria, tuberculosis, and HIV/AIDS whose progression can quickly result in death.[19] These among others, like underestimation of the disease burden, have resulted in insufficient resource allocation to schsitosomiasis research and control.[20]

Schistosomiasis in Women of Reproductive Age

Women, like any other population group, are susceptible to *Schistosoma* infections in endemic areas with prevalence ranging from 5 to 67%.[21,22] The occurrence of schistosomiasis in women in sub-Saharan Africa has been known since antiquity,[23–31] with most of the pathology associated with female genitalia. While most of the earlier reports comprised cross-sectional autopsy and surgical specimen studies, there have been considerable increase in community-based studies on female genital schistosomiasis in the last decade.[32–35] Kjetland *et al.*[36] in their comprehensive review had identified the cervix, vagina, fallopian tubes, ovary, and uterus as the most common gynecological predilection sites for schistosomiasis in women with vaginal discharge, pelvic discomfort, sandy patches in mucosa, contact bleeding, and edema as some of the symptoms mostly associated with infections. However, with the ever increasing evidences of female genital schistosomiasis and associated discomfort symptoms, none of such studies had addressed situations in pregnant women who may be liable to greater discomforts as a result of their conditions.

Epidemiological Data on Maternal Schistosomiasis in Sub-Saharan Africa

Schistosomiasis continues to plague the health of all population groups in endemic regions. There are growing concerns on occurrence of the disease in populations initially thought not to be at risk groups with the adult population dominating these groups. While a relatively more attention regarding epidemiological studies has been given to infant and preschool children (another thought not to be at risk group) in the last decades, data are still scarce on maternal schistosomiasis in the tropics. It is therefore not surprising that most of the data presented in this review (Table 1) were not solely focused on schistosomiasis, but in relation to other parasitic or infectious diseases. Compared with 838 studies on school children extrapolated from Schur *et al.*[2] (between 2000 and 2010), it is undeniable that epidemiological data on schistosomiasis during pregnancy are grossly scanty in sub-Saharan Africa. To worsen the situation, Liberia (58.3%) and other countries with very high pediatric schistosomiasis endemicity, such as Burkina Faso (50.2%), Cote d'Ivoire (41.8%), Sierra Leone (57.5%), Benin (46.0%), and Guinea (46.4%),[2] have presented no data for maternal schistosomiasis. With an incidence of infection ranging from 2.5–63.5% in pregnant women (Table 1) and a foreseeable gradual increase with time (Fig. 1), if serious intervention is not adopted, the scaling-up of the global burden of the disease may be inevitable bearing in mind the addictive effects of infection on the growing fetus and neonates.

Does Pregnancy Increase Severity of *Schistosoma* infection?

Pregnancy is known to cause immunological and hormonal alterations.[52] The increased secretion in pregnancy hormones with the gestational age significantly modulates the immunological shift that occurs during pregnancy.[53] The activation of Th2 immune response is caused by progesterone and other placental products such as prostaglandin E2;[54] *Schistosoma*-induced pathology may be exacerbated due to Th2 polarization during pregnancy.[55]

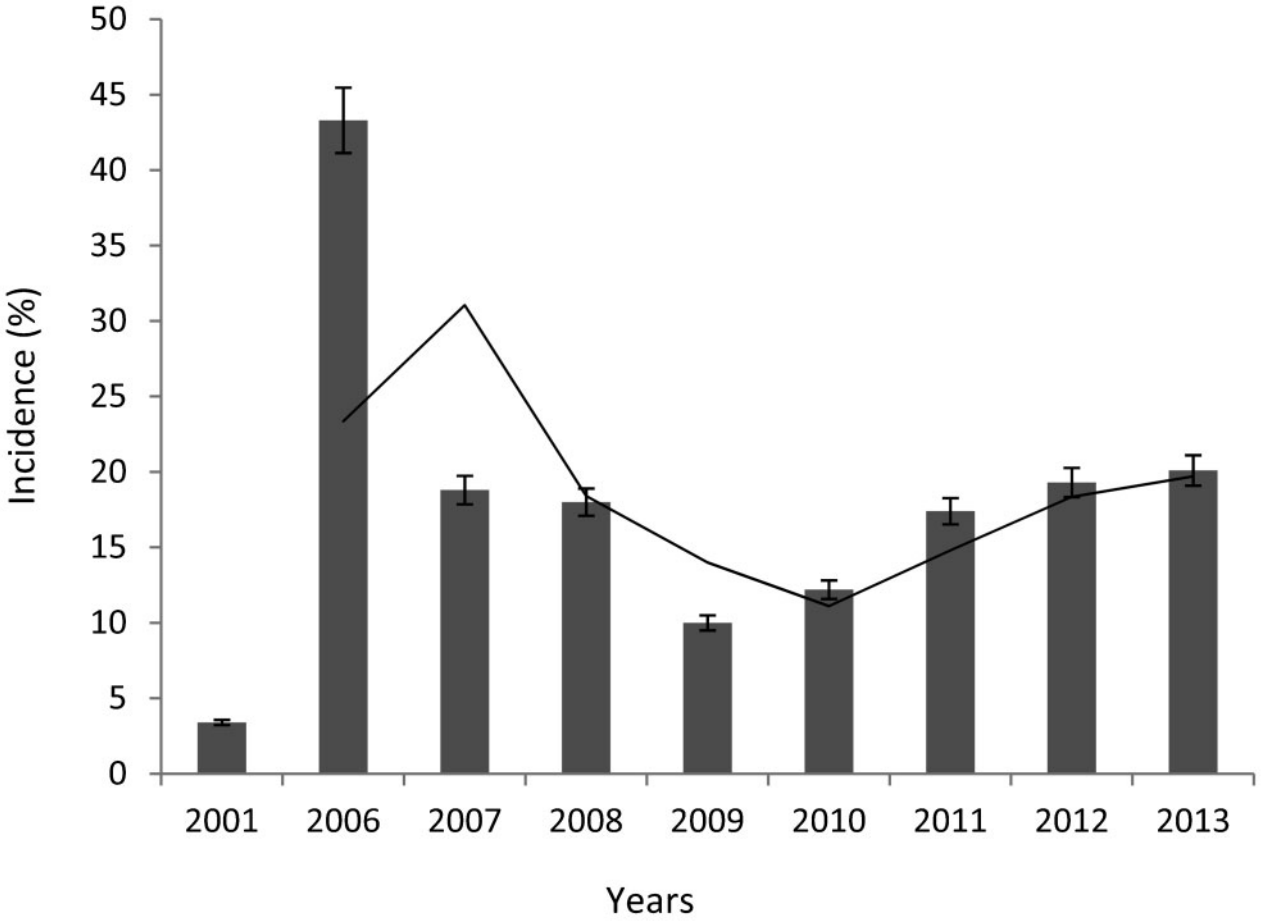

Figure 1 Incidence of schistosomiasis in sub-Saharan Africa (2001–2013).

Schistosome egg granuloma and a $CD4^+$ T cell-mediated delayed type hypersensitivity is the major cause of morbidity in schistosomiasis[56] with granulomatous inflammation and disease severity correlating with the balance between T helper 1 (Th1) and Th2 cytokine expression.[57] Large granuloma lesions and severe morbidity are associated with a Th2-dominated cytokine response, while Th1-dominant response is found associated with minimal lesions.[58] Like other infectious and parasitic agents, the disease burden as a result of *Schistosoma* infection is more pronounced in primigravid mothers.[38,51] However, contrary to other

Table 1 Epidemiological studies on maternal schistosomiasis in sub-Saharan Africa (2001–2013)

Country	Location	Parasite species	Sample size (*n*)	Prevalence (%)	Year	Reference
Nigeria	Bauchi, Jos, and Eku Delta state (urban)	*S. mansoni*	816	3.4	2001	Egwunyenga *et al.*[37]
Tanzania	Ukerewe Island (rural)	*S. mansoni*	972	63.5	2006	Ajanga *et al.*[38]
Mali	Banconi (urban)	*S. haematobium*	190	23.0	2006	Ayoya *et al.*[39]
Uganda	Entebbe (semi-urban)	*S. mansoni*	2507	18.3	2007	Muhangi *et al.*[40]
Uganda	Entebbe (semi-urban)	*S. mansoni*	2507	18.0	2008	Hillier *et al.*[41]
Uganda	Entebbe (semi-urban)	*S. mansoni*	2507	18.3	2009	Woodburn *et al.*[42]
Tanzania	Dar es Salaam (urban)	*S. mansoni*	971	1.7	2009	Kawai *et al.*[43]
Ghana	Kassena-Nankana District (semi-urban)	*S. mansoni*	190	12.3	2010	Fuseini *et al.*[44]
Gabon	Lambaréné (semi-rural)	*S. haematobium*	388	12.0	2010	Adegnika *et al.*[45]
Malawi	Machinga District (semi-urban)	*S. haematobium*	1772	32.3	2011	Thigpen *et al.*[46]
		S. mansoni	848	2.5	2011	
Sudan	ArabaWaeshreen Hospital, Geizera (rural)	*S. mansoni*	292	14.8	2012	Khalid *et al.*[47]
Nigeria	Umuleri, Aguleri, Anam, and Nzam (semi-urban)	*S. haematobium*	172	23.8	2012	Eyo *et al.*[48]
Gabon	Lambaréné and Fougamou (semi-rural)	*S. haematobium*	902	9.0	2013	Basra *et al.*[49]
Kenya	Msambweni (rural)	*S. haematobium*	696	30.6	2013	Fairley *et al.*[50]
Nigeria	Yewa North (rural)	*S. haematobium*	313	20.8	2013	Salawu and Odaibo[51]

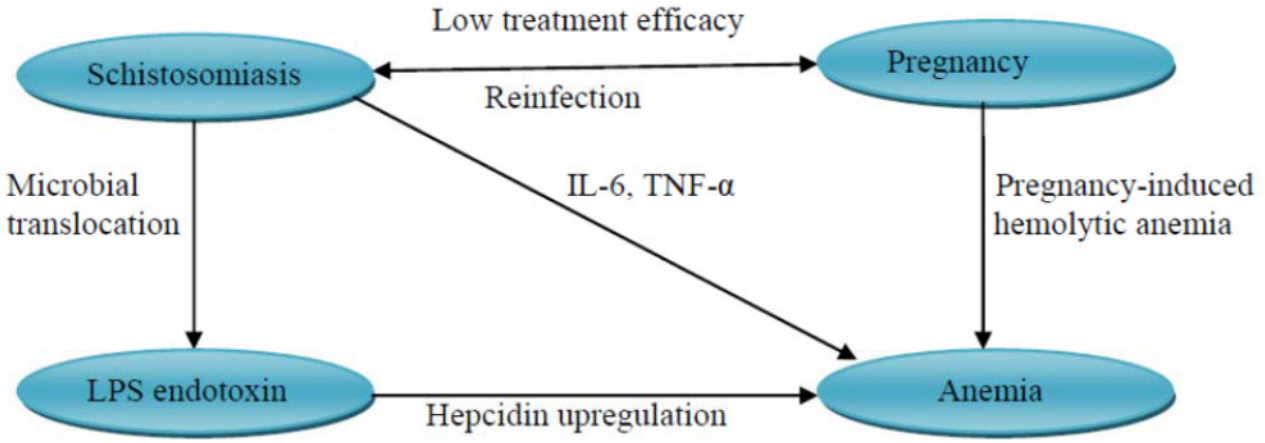

Figure 2 Schematic representation of schistosomiasis-associated anemia during pregnancy.

diseases, the disease burden tends to reduce with the gestational age, as intensity of infection has been reported to be lower in women in their late pregnancy.[51] The effect of more frequent micturition significantly lowering the intensity of infection in late pregnancy has been emphasized.[51] Although the increased secretion of progesterone and other reproductive hormones are known to increase susceptibility to infection, frequent micturition rate as a result of marked physiological changes in third trimester pregnancy seems to overshadow the hormonal influence. However, quantifying the disease burden by mere egg excretion rates is not enough to arrive at a reasonable conclusion. In fact, in *Schistosoma* chronic infection, very few eggs are known to be excreted with the majority of the eggs inducing granulomatous inflammatory response. Therefore, the pro-inflammatory immune cytokines associated with the disease progression and anemia are more reliable in quantifying *Schistosoma*-induced morbidities during pregnancy.

A cohort study among Ugandan pregnant women has further stressed a possible decrease in efficacy of praziquantel, the mainstay drug of choice for schistosomiasis during pregnancy.[59] The study reported a significant boost in levels of IgG1, IgG2, IgG3, and IgG4 against *Schistosoma* adult worm antigen at 61 weeks post-treatment compared to the placebo group. However, in comparing the antibodies boosting potential of praziquantel in pregnant women and 6-week post-delivery women (non-pregnant women), suppression in antibodies level against *Schistosoma* adult worm and *Schistosoma* soluble egg antigen was observed in pregnant women. This and other aforementioned data suggest serious implications for reinfection and more difficulties in the control of the disease during pregnancy.

Maternal Schistosomiasis and Adverse Pregnancy Outcomes

Anemia associated with chronic diseases is one of the proposed mechanisms of schistosomiasis-mediated adverse birth outcomes.[9] It is believed to be the result of the effects of pro-inflammatory cytokines that are produced in response to disease agents.[60] The upregulation of tumor necrosis factor-alpha causes decrease in the production of erythropoietin, which is responsible for bone marrow erythropoietic response,[44] thus disrupting red blood cell production and longevity.[9] Another mechanism known to cause decrease in iron bioavailability is the upregulation of hepcidin in response to IL-6 (a *Schistosoma*-associated cytokine), which raises the iron sequestration rate in storage form such as ferritin in the reticuloendothelial.[61,62]

There is lots of convincing evidence of schistosomiasis involvement in inducing an anemic condition in pregnant women with most of the anemic-associated morbidity more pronounced in heavily infected pregnant women population.[38,39,44] This is important as anemia has been implicated in maternal death and low birth weight.[63,64] A recent study among Philippine pregnant women has also implicated schistosomiasis in elevated maternal and placental compartment endotoxin levels.[65] Microbial translocation due to schistosome egg-induced pathology in the gut has been reported as the cause of increase in plasma levels of lipopolysaccharide endotoxin,[66] which has also been shown to induce an anemic condition.[67] It is evident from all of these studies that schistosomiasis-induced morbidity during pregnancy is complex, employing both direct and indirect routes in the pathogenesis (Fig. 2).

Transplacental Transmission and Neonatal Health

Both pregnancy and *Schistosoma* infection collectively cause downregulation in Th1 immune response and a possible increase in susceptibility to other infectious agents may arise. Increase in the burden of infectious agent in pregnant women can promote easy transmission to the growing fetus, especially in infections that employ placental route. Although the stage of *Schistosoma* species in human seems not to

have link with the placenta, studies have revealed, however, that transplacental transmission of schistosomes may be possible.[68,69] A recent study on the murine model showed that maternal infection is associated with increased placenta and cord blood inflammatory responses.[70] Several studies on human populations also reported *in utero* T and B lymphocytes sensitization to *Schistosoma* antigens in uninfected neonates born to chronically infected mothers.[71–74] A recent study has shown that alteration of fibrosis-associated molecules in the newborn of infected mothers has broad implications for the health of the fetus.[75]

There are also conflicting reports on the influence of maternal schistosomiasis on the efficacy of vaccines in newborns. Antenatal *Schistosoma* infections have been found to be associated with impaired Hib (*Haemophilus influenzae* type B vaccine) efficacy and reduced cell-mediated immunity responses to Bacillus Calmette–Guerin vaccine and tetanus toxoid in Kenyan infants.[76] While a study from Egypt showed significant association between maternal schistosomiasis and immune response of infants to hepatitis B vaccination,[77] another study in the same region reported otherwise.[78]

Hurdle in Treatment and Implication for Control

The WHO recommended the use of praziquantel during pregnancy[79] owing to the deleterious effects *Schistosoma* parasites could have on specific organs, maternal anemia, fetal growth, and perinatal mortality coupled with the evidences of improved infants' responses to immunization as earlier discussed. The justification for this recommendation was also due to lack of records on the side effects of the drug during pregnancy and no evidence of praziquantel fetal toxicity in animal models has been reported as at the time of the consultation.[80] However, the advocacy for treatment of pregnant women over the last decade has been insufficient, thus resulting in the stasis of the pharmaceutical sector to re-license and re-label praziquantel and largely blocking its use on pregnant women.

The need to conduct randomized control trials became paramount as no such study has been conducted before the recommendation. The only randomized, double-blind control trial[81] conducted has, however, called for the review of WHO recommendation owning to potential benefit *Schistosoma* infection, during pregnancy, can confer on the neonate. For example, the episodes of infantile eczema recorded in children of treated pregnant women.[82] The study further stressed that the major morbidity (i.e. anemia) often attributed to maternal schistosomiasis ruling out malaria and hookworm infections is not significant in single infection by schistosomes. Thus, it was hypothesized that '(1) maternal and childhood infections reduce the effectiveness of childhood immunizations and increase susceptibility to viral and bacterial infectious diseases, while reducing the incidence of diseases mediated by poorly-regulated inflammatory responses and (2) treatment of maternal and childhood helminth infection improves the effectiveness of childhood immunizations and modulates disease incidence in childhood, with both beneficial and detrimental effects'.[81]

Conclusions

The global burden of schistosomiasisis is underestimated as morbidities in fetus and neonate were not always considered. Recent studies on *Schistosoma*-associated burden and benefit during pregnancy are now posing a dilemma on whether to administer drugs or not during pregnancy. This question is clearly difficult to address now giving the various evidence-based studies supporting each opinion. A careful risk–benefit assessment is solicited after many unbiased randomized control trials are carried out in different parts of endemic countries. Since this could take some time, a suggested best approach towards the management of the disease is to prevent infection before and during pregnancy. This can be achieved through preventive chemotherapy in all women of reproductive age. The impact of education has also been emphasized in one of our studies among pregnant women in Nigeria.[7] Intensive education and training about transmission and morbidity associated with infection incorporated in antenatal programs will help as well. More epidemiological studies on maternal schistosomiasis across sub-Saharan Africa regions and development of predictive maps that will put into consideration all the other groups of population at risk will help in providing an accurate estimate of infection for effective management and control.

Instead of further adoption of mass chemotherapy which is often ineffective as more than 50% of the population at risk is not usually treated, case finding and targeted chemotherapy should be adopted.[83] This will help to conserve the limited resources and also channel control on often neglected populations of infants, preschool children, and pregnant women. Just as the development of appropriate pediatric formulation of praziquantel is ongoing,[84] revised licensing and improved formulation for maternal use is also strongly advocated.

Disclaimer Statements

Contributors The following are acknowledged for making available their articles: Professor Simon Brooker — Department of Infectious and Tropical Disease, London School of Hygiene and Tropical

Medicine, London; Professor Peter Hotez — Head, Section of Pediatric Tropical Medicine Baylor College of Medicine; Dr Emily McDonald — Department of Pediatrics Center for International Health Research, Rhode Island Hospital, Brown University School of Medicine; and Dr Joachim Voss — University of Washington. Also we acknowledge the two anonymous reviewers whose constructive criticisms have greatly improved the quality of this manuscript.

Funding None.

Conflicts of interest None.

Ethics approval None.

References

1 Chitsulo L, Engels D, Montresor A, Savioli L. The global status of schistosomiasis and its control. Acta Trop. 2000;77:41–51.
2 Schur N, Hürlimann E, Garba A, Traoré MS, Ndir O, Ratard RC. Geostatistical model-based estimates of schistosomiasis prevalence among individuals aged <20 years in West Africa. PLoS Negl Trop Dis. 2011;5:e1194.
3 Salawu OT, Odaibo AB. Preliminary study on ecology of *Bulinus jousseaumei* snail in *Schistosoma haematobium* endemic rural community of Nigeria. Afr J Ecol. 2012;51:441–6.
4 Okoli EI, Odaibo AB. Urinary schistosomiasis among school children in Ibadan, an urban community in Southwestern Nigeria. Trop Med Int Health. 1999;4:308e15.
5 Oladejo SO, Ofoezie IE. Unabated schistosomiasis transmission in Erinle river Dam, Osun state, Nigeria: evidence of neglect of environmental effects of development project. Trop Med Int Health. 2006;11:843e50.
6 Ugbomoiko US, Ofoezie IE, Okoye IC, Heukelbach J. Factors associated with urogenital schistosomiasis in two peri-urban communities in southwestern Nigeria. Ann Trop Med Parasitol. 2010;104:409–19.
7 Salawu OT, Odaibo AB. Schistosomiasis transmission; socio-demographic, knowledge and practices as transmission risk factors in pregnant women. J Parasit Dis. 2014, 18 April [Epub ahead of print]. doi 10.1007/s12639-014-0454-2.
8 Stothard JR, Gabrielli A. Schistosomiasis in African infants and preschool children: to treat or not to treat? Trends Parasitol. 2007;23:83e6.
9 Friedman JF, Mital P, Kanzaria HK, Olds GR, Kurtis JD. Schistosomiasis and pregnancy. Trends Parasitol. 2007;23:159–64.
10 Hillyer GV, Tsang VC, Vivas-Gonzalez BE, Noh J, Ahn LH, Vorndam V. Age-specific decrease in seroprevalence of schistosomiasis in Puerto Rico. Am J Trop Med Hyg. 1999;60:313–8.
11 Jordan P. From Katayama to the Dakhla Oasis: the beginning of epidemiology and control of bilharzia. Acta Trop. 2000;77:9–40.
12 Laamrani H, Khallaayoune K, Madsen H, Mahjour J, Gryseels B. New challenges in schistosomiasis control in Morocco. Acta Trop. 2000;77:61–7.
13 Engels D, Chitsulo L, Montresor A, Savioli L. The global epidemiological situation of schistosomiasis and new approaches to control and research. Acta Trop. 2002;82:139–46.
14 Utzinger J, Zhou XN, Chen MG, Bergquist R. Conquering schistosomiasis in China: the long march. Acta Trop. 2005;96:69–96.
15 Stothard JR, Chitsulo L, Kristensen TK, Utzinger J. Control of schistosomiasis in sub-Saharan Africa: progress made, new opportunities and remaining challenges. Parasitology 2009;136:1665–75.
16 Lengeler C, Utzinger J, Tanner M. Questionnaires for rapid screening of schistosomiasis in sub-Saharan Africa. Bull World Health Organ. 2002;80:235–42.
17 Hotez PJ, Fenwick A. Schistosomiasis in Africa: an emerging tragedy in our new global health decade. PLoS Negl Trop Dis. 2009;3:e485.
18 Hotez PJ, Brindley PJ, Bethony JM, King CH, Pearce EJ, Jacobson J. Helminth infections: the great neglected tropical diseases. J Clin Invest. 2008;118:1311–21.
19 King CH, Bertino AM. Asymmetries of poverty: why global burden of disease valuations underestimate the burden of neglected tropical diseases. PLoS Negl Trop Dis. 2008;2:e209.
20 Bergquist R, Utzinger J, McManus DP. Trick or treat: the role of vaccines in integrated schistosomiasis control. PLoS Negl Trop Dis. 2008;2:e244.
21 Down JA, Mguta C, Kaatano GM, Mitchell KB, Bang H, Simplice H, *et al*. Urogenital schistosomiasis in women of reproductive age in Tanzania's Lake Victoria region. Am J Trop Med Hyg. 2011;84:364–9.
22 Seto EY, Sousa-Figueiredo JC, Betson M, Byalero C, Kabatereine NB, Stothard JR. Patterns of intestinal schistosomiasis among mothers and young children from Lake Albert, Uganda: water contact and social networks inferred from wearable global positioning system data loggers. Geospat Health. 2012;7:1–13.
23 Williams AO. Pathology of schistosomiasis of the uterine cervix due to *S. haematobium*. Am J Obstet Gynecol. 1967;98:784–91.
24 Gelfand M, Ross MD, Blair DM, Weber MC. Distribution and extent of schistosomiasis in female pelvic organs, with special reference to the genital tract, as determined at autopsy. Am J Trop Med Hyg. 1971;20:846–9.
25 Edington GM, Nwabuebo I, Junaid TA. The pathology of schistosomiasis in Ibadan, Nigeria with special reference to the appendix, brain, pancreas and genital organs. Trans R Soc Trop Med Hyg. 1975;69:153–6.
26 Loubière R, Ette M, Nozais JP, Emeric R, Ehouman A, Dago AA, *et al*. Bilharziosis in Ivory Coast from the perspective of the laboratory of pathological anatomy. Méd Afr Noire. 1977;24:453–61.
27 Bayo S, Mamantou P, Samassekou M. Bilharziasis of the uterine cervix in Mali. Afr Méd. 1981;19:252–6.
28 Helling-Giese G, Sjaastad A, Poggensee G, Eyrun EF, Ritcher J, Chitsulo L, *et al*. Female genital schistosomiasis (FGS): relationship between gynecological and histopathological findings. Acta Trop. 1996;62:257–7.
29 Kjetland EF, Poggensee G, Helling-Giese G, Ritcher J, Sjaastad A, Chitsulo L, *et al*. (1996) Female genital schistosomiasis due to *Schistosoma haematobium*.Clinical and parasitological findings in women in rural Malawi. Acta Trop. 1996;62:239–55.
30 Leutscher P, Raharisolo C, Pecarrere JL, Ravaoalimalala VE, Serieye J, Rasendramino M, *et al*. *Schistosoma haematobium* induced lesions in the female genital tract in a village in Madagascar. Acta Trop. 1997;66:27–33.
31 Swai B, Poggensee G, Mtweve S, Krantz I. Female genital schistosomiasis as an evidence of a neglected cause for reproductive ill-health: a retrospective histopathological study from Tanzania. BMC Infect Dis. 2006;6:134.
32 Poggensee G, Kiwelu I, Weger V, Gõppner D, Diedrich T, Krantz I, *et al*. Female genital schistosomiasis of the low-ergenital tract: prevalence and disease-associated morbidity in northern Tanzania. J Infect Dis. 2000;181:1210–3.
33 Kjetland EF, Ndhlovu PD, Mduluza T, Gomo E, Gwanzura L, Mason PR, *et al*. Simple clinical manifestations of genital *Schistosoma haematobium* infection in rural Zimbabwean women. Am J Trop Med Hyg. 2005;72:311–9.
34 Kjetland EF, Kurewa EN, Ndhlovu PD, Midzi N, Gwanzura L, Mason PR, *et al*. Female genital schistosomiasis – a differential diagnosis to sexually transmitted disease: genital itch and vaginal discharge as indicators of genital *S. haematobium* morbidity in a cross-sectional study in endemic rural Zimbabwe. Trop Med Int Health. 2008;13:1509–17.
35 Leutscher PD, Ramarokoto CE, Hoffmann S, Jensen JS, Ramaniraka V, Randrianasolo B, *et al*. Coexistence of urogenital schistosomiasisand sexually transmitted infection in women and men living in an area where *Schistosoma haematobium* is endemic. Clin Infect Dis. 2008;47:775–82.
36 Kjetland EF, Leutscher PD, Ndhlovu PD. A review of female genital schistosomiasis. Trends Parasitol. 2012;28:58–65.
37 Egwunyenga AO, Ajayi JA, Nmorsi OP, Duhlinska-Popova DD. Plasmodium/intestinal helminth co-infections among pregnant Nigerian women. Mem Inst Oswaldo Cruz. 2001;96:1055–9.
38 Ajanga A, Lwambo NJ, Blair L, Nyandindi U, Fenwick A, Brooker S. *Schistosoma mansoni* in pregnancy and associations

with anemia in northwest Tanzania. Trans R Soc Trop Med Hyg. 2006;100:59–63.
39 Ayoya MA, Spiekermann-Brouwer GM, Traoré AK, Stoltzfus RJ, Garza C. Determinants of anemia among pregnant women in Mali. Food Nutr Bull. 2006;27:3–11.
40 Muhangi L, Woodburn P, Omara M, Omoding N, Kizito D, Mpairwe H, *et al*. Associations between mild-to-moderate anemia in pregnancy and helminth, malaria and HIV infection in Entebbe, Uganda. Trans R Soc Trop Med Hyg. 2007;101:899–907.
41 Hillier SD, Booth M, Muhangi L, Nkurunziza P, Khihembo M, Kakande M, *et al*. *Plasmodium falciparum* and helminth coinfection in a semiurban population of pregnant women in Uganda. J Inf Dis. 2008;198:920–7.
42 Woodburn PW, Muhangi L, Hillier S, Ndibazza J, Namujju PB, Kizza M, *et al*. Risk factors for helminth, malaria, and HIV infection in pregnancy in Entebbe, Uganda. PLoS Negl Trop Dis. 2009;3:e473.
43 Kawai K, Saathoff E, Antelman G, Msamanga G, Fawzi WW. Geophagy (soil-eating) in relation to anemia and helminth infection among HIV-infected pregnant women in Tanzania. Am J Trop Med Hyg. 2009;80:36–43.
44 Fuseini G, Edoh D, Kalifa BG, Hamid AW, Knight D. Parasitic infections and anaemia during pregnancy in the Kassena-Nankana district of Northern Ghana. J Publ Health Epidemiol. 2010;2:48–52.
45 Adegnika AA, Ramharter M, Agnandji ST, Ngoa UA, Issifou S, Yazdanbahksh M, *et al*. Epidemiology of parasitic co-infections during pregnancy in Lambaréné, Gabon. Trop Med Intl Health. 2010;15:1204–9.
46 Thigpen MC, Filler SJ, Kazembe PN, Parise ME, Macheso A, Campbell CH, *et al*. Associations between peripheral *Plasmodium falciparum* malaria parasitemia, human immunodeficiency virus, and concurrent helminthic infection among pregnant women in Malawi. Am J Trop Med Hyg. 2011;84:379–85.
47 Khalid A, Abdelgadir MA, Ashmaig A, Ibrahim AM, Ahmed AA, Adam I. *Schistosoma mansoni* infection among prenatal attendees at a secondary-care hospital in central Sudan. Int J Gynecol Obstet. 2012;116:10–2.
48 Eyo JE, Onyishi GC, Okafor FC. Urinary schistosomiasis among pregnant women in some endemic tropical semi-urban communities of Anambra State. Nigeria Trop Biomed. 2012;29:1–5.
49 Basra A, Mombo-Ngoma G, Melser MC, Diop DA, Würbel H, Mackanga JR, *et al*. Efficacy of mefloquine intermittent preventive treatment in pregnancy against *Schistosoma haematobium* infection in Gabon: a nested randomized controlled assessor-blinded clinical trial. Clin Inf Dis. 2013;56:68–75.
50 Fairley JK, Bisanzio D, King CH, Kitron U, Mungai P, Muchiri E, *et al*. Birth weight in offspring of mothers with high prevalence of helminth and malaria infection in coastal Kenya. Am J Trop Med Hyg. 2013;88:48–53.
51 Salawu OT, Odaibo AB. Schistosomiasis among pregnant women in rural communities in Nigeria. Int J Gynecol Obstet. 2013;122:1–4.
52 Abdoli A, Pirestani M. Are pregnant women with chronic helminth infections more susceptible to congenital infections? Front Immunol. 2014;5:1–4.
53 Robinson DP, Klein SL. Pregnancy and pregnancy-associated hormones alter immune responses and disease pathogenesis. Horm Behav. 2012;62:263–71.
54 Kelly RW, Critchley HO. A T-helper-2 bias in decidua: the prostaglandin contribution of the macrophage and trophoblast. J Reprod Immunol. 1997;33:181–7.
55 Farah IO, Langoi D, Nyaundi J, Hau J. Schistosome-induced pathology is exacerbated and Th2 polarization is enhanced during pregnancy. *In Vivo*. 2007;21:599–602.
56 Boros DL. The role of cytokines in the formation of the schistosome egg granuloma. Immunobiology. 1994;191:441–50.
57 Kaplan MH, Wurster AL, Grusby MJ. A signal transducer and activator of transcription (Stat) 4-independent pathway for the development of T helper type 1 cells. J Exp Med. 1998;188: 1191–6.
58 Wynn TA, Cheever AW. Cytokine regulation of granuloma formation in schistosomiasis. Curr Opin Immunol. 1995;7:505–11.
59 Tweyongyere R, Mawa PA, Emojong NA, Mpairwe H, Jones FM, Duong T, *et al*. Effect of praziquantel treatment of *Schistosoma mansoni* during pregnancy on intensity of infection and antibody responses to schistosome antigens: results of a randomised, placebo-controlled trial. BMC Inf Dis. 2009;9:32.
60 Means RT, Jr. The anemia of infection. Best Pract Res Clin Haematol. 2000;13:151–62.
61 Ganz T. The role of hepcidin in iron sequestration during infections and in the pathogenesis of anemia of chronic disease. Isr Med Assoc J. 2002;4:1043–5.
62 Ganz T. Hepcidin, a key regulator of iron metabolism and mediator of anemia of inflammation. Blood. 2003;102:783–8.
63 Abouzhar C. Maternal mortality overview. In: Murray C, Lopez A, editors. Health dimensions of sex and reproduction. Boston, MA: Harvard University Press; 1998. p. 111–64.
64 Murray C, Shibuya K. Low birth weight. In: Murray C, Lopez A, editors. Health dimensions of sex and reproduction. Boston, MA: Harvard University Press; 1998; p. 389–28.
65 McDonald EA, Pond-Tor S, Jarilla B, Sagliba MJ, Gonzal A, Amoylen AJ, *et al*. Schistosomiasis japonica during pregnancy is associated with elevated endotoxin levels in maternal and placental compartments. J Inf Dis. 2014;209:468–72.
66 Onguru D, Liang Y, Griffith Q, Nikolajczyk B, Mwinzi P, Ganley-Leal L. Human schistosomiasis is associated with endotoxemia and Toll-like receptor 2- and 4-bearing B cells. Am J Trop Med Hyg. 2011;84:321–4.
67 Kemna K, Pickkers P, Nemeth E, van der Hoeven H, Swinkels D. Time-course analysis of hepcidin, serum iron, and plasma cytokine levels in humans injected with LPS. Blood. 2005; 106:1864–6.
68 Willingham AL 3rd, Johansen MV, Bøgh HO, Ito A, Andreassen J, Lindberg R, *et al*. Congenital transmission of *Schistosoma japonicum* in pigs. Am J Trop Med Hyg. 1999;60:311–2.
69 Iburg T, Balemba OB, Danizer V, Leifsson PS, Johansen MV. Pathogenesis of congenital infection with *Schistosoma japonicum* in pigs. J Parasitol. 2002;88:1021–4.
70 Kurtis JD, Higashi A, Wu HW, Gundogan F, McDonald EA, Sharma S, *et al*. Maternal schistosomiasis japonica is associated with maternal, placental, and fetal inflammation. Infect Immun. 2011;79:1254–61.
71 Camus D, Carlier Y, Bina J, Borojevic R, Prata A, Capron A. Sensitization to *Schistosoma mansoni* antigen in uninfected children born to infected mothers. J Infect Dis. 1976;134: 405–8.
72 Novato-Silva E, Gazzinelli G, Colley D. Immune responses during human schistosomiasis mansoni. XVIII. Immunologic status of pregnant women and their neonates. Scand J Immunol. 1992;35:429–37.
73 Malhotra I, Ouma J, Wamachi A, Kioko J, Mungai P, Omollo A, *et al*. *In utero* exposure to helminth and mycobacterial antigens generates cytokine responses similar to that observed in adults. J Clin Invest. 1997;99:1759–66.
74 King CL, Malhotra I, Mungai P, Wamachi A, Kioko J, Ouma JH, *et al*. B cell sensitization to helminthic infection develops *in utero* in humans. J Immunol. 1998;160:3578–84.
75 McDonald EA, Cheng L, Jarilla B, Sagliba MJ, Gonzal A, Amoylen AJ, *et al*. Maternal infection with *Schistosoma japonicum* induces a profibrotic response in neonates. Infect Immun. 2014;82:350–5.
76 Malhotra I, Kioko J, Mungai P, Muchiri E, Wamachi A, King CL. Antenatal helminth infections are associated with impaired Hib vaccine efficacy in Kenyan infants. In: Proceedings of Keystone Symposia: Immunological Mechanisms of Vaccination; 2010 Oct 27–Nov 1; Seattle, WA, USA. Keystone Symposia: Silverthorne, CO, USA, 2010. Abstr 250.
77 Ghaffar YA, Kamel M, El-Sobky M, Bahnasy R, Strickland GT. Response to hepatitis B vaccine in infants born to mothers with schistosomiasis. Lancet. 1989;334:272.
78 Bassily S, Kotkat A, Hyams K, Youssef FG, El-Masry NA, Arthur R, *et al*. Immunogenicity of recombinant hepatitis B vaccine among infants of mothers with active schistosomiasis. Am J Trop Med Hyg. 1997;57:197–9.
79 World Health Organization (WHO) Expert Committee. Prevention and control of schistosomiasis and soil transmitted helminthiasis. World Health Organ Tech Rep Ser. 2002;912:i-vi, 1–57.
80 Elliott AM, Ndibazza J, Mpairwe H, Muhangi L, Webb EL, Kizito D, *et al*. Treatment with anthelminthics during pregnancy: what gains and what risks for the mother and child? Parasitol. 2011;138:1499–507.
81 Elliott AM, Kizza M, Quigley MA, Ndibazza J, Nampijja M, Muhangi L, *et al*. The impact of helminthes on the response to immunization and on the incidence of infection and disease in

childhood in Uganda: design of a randomized, double-blind, placebo-controlled, factorial trial of deworming interventions delivered in pregnancy and early childhood [ISRCTN328 49447]. Clin Trials. 2007;4:42–57.
82 Elliott AM, Mpairwe H, Quigley MA, Nampijja M, Muhangi L, Oweka-Onyee J, *et al.* Helminth infection during pregnancy and development of infantile eczema. JAMA. 2005;294:2032–4.
83 Gray DJ, McManus DP, Li Y, Williams GM, Bergquist R, Ross AG. Schistosomiasis elimination: lessons from the past guide the future. Lancet Infect Dis. 2010;10:733–6.
84 Stothard JR, Sousa-Figueiredo, JC, Betson M, Bustinduy A, Reinhard-Rupp J. Schistosomiasis in African infants and preschool children: let them now betreated! Trends Parasitol. 2013;29:197–205.